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Acute Kidney Injury in Neonates Admitted to a Low-Resource Neonatal Intensive Care Unit in Lusaka, Zambia

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Abstract

Background: Neonatal acute kidney injury (nAKI) has been reported to be common among neonates admitted to the Neonatal Intensive Care Unit (NICU) and is associated with increased mortality and prolonged duration of hospital stay. However, data on this entity from sub-Saharan Africa are scanty.

Objectives: This study aimed to assess the burden, risk factors, and short-term outcomes of nAKI in neonates admitted to a low-resource NICU in Zambia.

Design: The design of the study is a prospective cohort study.

Setting: The setting of this study was the NICU at the Women and Newborn Hospital of the University Teaching Hospitals (WNBH-UTHs).

Patients: In total, 322 neonates who were admitted to the NICU between November 2021 and December 2022.

Methods: A serum creatinine was determined on all patients at admission (within 24 hours), at 72 hours and day 7. The modified neonatal Kidney Disease: Improving Global Outcome (KDIGO) Criteria were used to define nAKI. Data were extracted using a predesigned form and analyzed using SPSS. A *P*-value less than .05 was considered statistically significant.

Results: The prevalence of nAKI was 13.7% (44/322). On multivariable regression analysis, antepartum hemorrhage (adjusted odds ratio [AOR] 5.58; 95% confidence interval [CI]: [1.62-19.13], $P=.007$), vomiting in the neonate (AOR 5.76; 95% CI: [1.10-30.32], $P=.04$), history of use of unit second-line antibiotics, meropenem (AOR 4.37; 95% CI: [1.97-9.69], $P<.001$), and ciprofloxacin (AOR 4.53; 95% CI: [1.22-16.84], $P=.02$) were associated with increased risk of nAKI. Acute kidney injury (AKI) was significantly associated with longer length of hospital stay and higher mortality ($P<.05$).

Limitations: The study did not use the urine output criteria to define nAKI and this may have led to an underestimation of nAKI prevalence. Additionally, kidney, ureter, and bladder ultrasound was not performed on any of the study participants.

Conclusion: AKI is common in neonates admitted to the NICU at WNBH-UTHs, and it is associated with a higher risk of mortality and prolonged length of hospital stay. Further studies among the various NICU sub-populations are needed to better characterize risks and outcomes.

Abrégé

Contexte: L'insuffisance rénale aiguë néonatale (IRAn) est fréquente chez les nouveau-nés admis aux unités de soins intensifs néonataux (USIN). L'IRAn est associée à une mortalité accrue et à un séjour prolongé à l'hôpital. Cependant, les données sur l'IRAn en Afrique subsaharienne sont rares.

Objectif: Évaluer les résultats à court terme de l'IRAn, de même que les facteurs de risque et le fardeau posé par la maladie, chez les nouveau-nés admis dans une unité de soins intensifs néonataux à faibles ressources de la Zambie.

Type d'étude: Étude de cohorte prospective.

Cadre: L'unité de soins intensifs néonataux du Women and Newborn Hospital of the University Teaching Hospitals (WNBH-UTHs).

Sujets: Trois cent vingt-deux (322) nouveau-nés admis à l'USIN entre novembre 2021 et décembre 2022.

Méthodologie: Une mesure de la créatinine sérique a été réalisée chez tous les patients à leur admission (dans les 24 heures), à 72 heures et au septième jour. Les critères d'une version modifiée pour l'insuffisance rénale néonatale du KDIGO (modified neonatal kidney Disease: Improving Global Outcome) ont été utilisés pour définir l'IRAn. Les données ont été extraites à l'aide d'un formulaire préconçu et analysées à l'aide du SPSS. Une valeur $P<0,05$ a été considérée comme statistiquement significative.

Résultats: La prévalence de l'IRAn était de 13,7 % (44/322). Selon l'analyze de régression multivariée, l'hémorragie antepartum (rapport de cote corrigé [RCC]: 5,58; IC 95 % [intervalle de confiance]: [1,62–19,13]; $P = 0,007$), les vomissements chez le nouveau-né [RCC: 5,76; IC 95 %: [1,10 – 30,32]; $P = 0,04$) et les antécédents d'utilization de méropénème, un antibiotique de deuxième ligne, (RCC: 4,37; IC à 95 %: [1,97 – 9,69]; $P < 0,001$) et de ciprofloxacine (RCC: 4,53; IC 95 %: [1,22 – 16,84]; $P = 0,02$) étaient associées à un risque accru d'IRAn; laquelle a été associée de façon significative à un séjour prolongé à l'hôpital et à une mortalité plus élevée ($P < 0,05$).
Limites: L'étude n'a pas utilisé la diurèse comme critère pour définir l'IRAn et cela pourrait avoir conduit à une sous-estimation de la prévalence. Aucun participant à l'étude n'avait subi d'échographie des reins, des uretères et de la vessie.
Conclusion: L'IRA est fréquente chez les nouveau-nés admis à l'USIN du WNBH-UTHs et elle a été associée à un séjour prolongé à l'hôpital ainsi qu'à un risque accru de mortalité. D'autres études avec différentes sous-populations de patients des USIN sont nécessaires afin de mieux caractériser les facteurs de risque et les résultats.

Keywords
acute kidney injury, neonate, neonatal intensive care unit, asphyxia, Zambia

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Introduction

Acute Kidney Injury (AKI) is defined as an acute deterioration in renal function and is marked by an increase in serum creatinine (SCr) associated with or without a reduction in the urine output with consequent derangement in fluid balance and electrolytes.[1,2] It is a complex syndrome whose manifestations range from mild injury to severe requiring renal replacement therapy.[3]

Neonates may be at increased risk of AKI for several reasons. Firstly, neonates admitted to the Neonatal Intensive Care Unit (NICU) suffer from conditions that may put them at greater risk of AKI. Examples of these various morbidities include sepsis, birth asphyxia, prematurity, and necrotising enterocolitis.[2] Secondly, various physiological characteristics of the neonatal kidneys increase the risk of AKI in the neonatal period. These include increased susceptibility to hypoperfusion, higher renal vascular resistance, increased plasma renin activity, and decreased sodium reabsorption in the proximal tubules.[3] The occurrence of this syndrome increases the risk of adverse outcomes among affected neonates.[4,5]

The neonatal population presents even more diagnostic challenges for the definition of AKI because the newborns' SCr level at birth mirrors the mother's creatinine level.[6] Over time, various definitions have been used for Neonatal Acute Kidney Injury (nAKI).[7] However, in line with the recent adoption of AKI consensus definitions, the modified neonatal Kidney Disease: Improving Global Outcome (KDIGO) criteria were formulated.[8] This definition allows better comparison of epidemiological and clinical trial findings, and was validated by the multicenter AWAKEN (Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates) study.[9,10] The modified neonatal KDIGO criteria define nAKI as a rise in the levels of SCr of more than 26.5 µmol/L or greater than 50% from the previous lowest value or a urine output of less than 1 mL/kg/h in a 24-hour period.[8]

The International AWAKEN study which involved more than 2000 neonates admitted in NICU from 24 sites in 4 countries revealed that the incidence of AKI in neonates was 30%.[9] This study also showed that the presence nAKI is associated with increased mortality and increased length of hospital stay. Depending on the patient sub-population and the definition of nAKI used, the incidence of AKI in the NICU varies greatly.[4,11] A review of various studies on neonatal AKI in the neonatal sub-population by Coleman et al[4] revealed that the incidence of nAKI ranges from 18% to 74%.

In many instances, AKI can be prevented, or at the very least, the initial tissue injury can be mitigated if patients at risk of this condition are identified early. Sadly, there is scanty information on the prevalence of nAKI. This poses a challenge for clinicians attempting to formulate treatment guidelines and primary prevention strategies. In addition, because the severity of neonatal AKI is not well described, it is difficult for many neonatal services to forecast requirements for the appropriate management of neonates with this entity.

We conducted a prospective observational study at the Women and Newborn Hospital (WNBH) NICU, a low-resource setting, to determine the burden, risk factors, and

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short-term outcomes of AKI in the neonates hospitalized there.

Materials and Methods

Study Design, Site, and Population

A prospective observational study was conducted from November 2021 to December 2022 to assess the burden, risk factors, and short-term outcomes of nAKI in neonates admitted to the NICU at the University Teaching Hospitals-Women and Newborn Hospital (UTHs-WNBH). We aimed to determine the prevalence, associated risk factors, and outcomes of AKI in neonates admitted to NICU.

The UTHs-WNBH NICU in Lusaka, Zambia, is a level II NICU. It is a national referral center for premature and critically ill neonates and has a capacity to accommodate 90 patients. There are approximately 4700 admissions per year to the NICU at UTHs-WNBH, and the leading causes of mortality are prematurity, birth asphyxia, and neonatal sepsis.

The study population consisted of neonates admitted to NICU at UTHs-WNBH. They included both neonates who were admitted directly from the labor ward/theater at UTHs-WNBH and neonates referred from other facilities within and outside Lusaka. Most term neonates with sepsis who are referred from various health facilities in the city are usually not admitted to the NICU at UTH-WNBH but are rather referred to the children's hospital.

Study Definitions, Inclusion and Exclusion Criteria

AKI: In this study, nAKI was defined and staged using KDIGO modified for neonates which is defined as the rise in the levels of SCr (≥26.5 µmol/L) or 50% or more from the previous lowest value.[9]

Change in SCr from baseline was calculated by dividing SCr at day 3 (72 hours)

by baseline SCr (admission creatinine) as shown below:

$$Change\ in\ Serum\ creatinine = \frac{Day\ 3\ serum\ Creatinine}{Admission\ serum\ creatinine}$$

The nAKI staging was done as shown below:

Stage 1: change in SCr from baseline ≥ 1.5 to 1.9 times
Stage 2: change in SCr from baseline ≥ 2.0 to 2.9 times
Stage 3: change in SCr from baseline ≥ 3.0 times

Included in the study were critically ill neonates admitted to NICU for any ailments and whose parents had given written informed consent. We excluded neonates who had obvious or confirmed congenital renal malformations, such as bladder exstrophy, and neonates who died within 72 hours of being admitted.

Sample Size Determination and Sampling Technique

Sample size was determined using the Cochran's sample size formula for surveys at 0.05 level of significance. In 2019, the total number of patients admitted to NICU at UTHs-WNBH was 4839 (ie, population at risk). The prevalence of AKI in NICU, in a study conducted in Tanzania, was 31.5%.[12] Based on this information, the sample size was determined to be 311 for a finite population where provision was made for a 10.0% rate for missing data/laboratory results.

Total enumerative sampling was used in this study. All neonates admitted to NICU at UTHs-WNBH who met the inclusion criteria and whose parents gave written informed consent, were enrolled into the study within 24 hours of admission, until the sample size was met. This was done after the neonate had been stabilized and parents / guardian counseled on the condition of the patient.

Data Collection

Parents were only invited to participate in the study after their child had been admitted, stabilized, and they had received counseling on the child's condition from the attending physician. Consent was obtained by either the study doctor or nurse. After informed written consent was obtained, participants were then enrolled onto the study. The study physician then conducted a physical examination of the patient and obtained information from the parents. Demographic, clinical, and laboratory data were also obtained from the neonates' files. All this information was entered onto a predesigned data extraction form. The information was then entered into an excel spreadsheet that was kept on a password-protected computer accessible to only essential study staff.

Blood for SCr levels was collected on the day of admission, on day 3 and on day 7 of admission. Neonates were followed-up until discharge or up to a total of 30 days to assess the short-term outcomes. The outcomes assessed were the development of nAKI as the primary outcome variable and mortality and length of hospital stay in NICU as secondary outcome variables.

Laboratory Data

After consent was obtained, 2 mL of peripheral venous blood was collected and placed into a heparinized vacutainer, within 24 hours of admission, and on days 3 and 7 by the principal investigator and 2 qualified nurses who were contracted as research assistants. The specimen was analyzed for SCr using Beckman Coulter AU480 analyzer which uses the principle of spectrophotometry. The SCr was measured using Kinetic Jaffe (compensated method) traceable to the Isotope Dilution Mass Spectrometry (IDMS) reference method and the reagent used was OSR6178.

Study Variables

The primary outcome (dependent) variable was the development of AKI which was determined by measuring SCr and defined using the modified neonatal KIDGO AKI criteria. The secondary study outcomes were length of hospital stay in days and mortality.

The Independent Variables assessed were the age of the neonate in days at admission, the sex of the neonate (male/female), the gestation age of the neonate at delivery (Using the date of the Last Normal Menstrual Period), and the age of the mother. Other independent variables noted were the birth weight in kilograms, the Apgar score at 5 minutes, the mode of delivery (either by spontaneous vaginal delivery, by cesarean section, or by vacuum extraction), and where the delivery occurred (at home, at clinic, or at UTH). The drugs administered during the course of admission were noted as was the diagnosis at admission to NICU. Any other diagnosis during course of the admission was considered as secondary diagnosis. Other treatments noted were the need for mechanical ventilation and the need for vasopressor support. The laboratory variables included the hemoglobin, platelets, and total white cell count.

Data Analysis

Data were collected using a predesigned data extraction form, entered into an excel spread sheet, and then transferred to the Statistical Package for Social Science (SPSS)™ version 27 for analysis. The data collected were coded and cleaned prior to analysis. Descriptive statistics were first analyzed to observe the characteristics of the variables. The outcome variable, AKI, was coded and converted into a binary outcome, for which frequencies and percentages were calculated. The chi-squared test was used to determine the relationship between AKI and independent factors, and Fisher's exact test was used when the chi-squared assumptions were not met. Univariable and multivariable logistic regression analyses were used to identify factors associated with AKI. The significance level was set at 5% with a confidence level of 95%. To create the final model, backward elimination logistic regression was used retaining all explanatory variables with a *P*-value less than .05.[13] The Hosmer and Lemeshow goodness-of-fit test was used to indicate a good-fitting model.

Ethical Considerations

Ethical clearance from the University of Zambia Biomedical Research Ethics Committee (UNZA/BREC, **REF. No. 1802-2021**) of the School of Medicine and from the National Health Research Authority (NHRA, **REF: NHREB00003/04/09/2021**) was obtained. Further permission was obtained from the management of UTH-WNBH and the head of the Neonatal Unit. Only patients for whom written informed consent was obtained were enrolled in the study. All study participants were given a unique study identification number so as to enable de-identification of participant data. The completed data collection forms were kept in a locked cabinet only accessible to key study team members.

Results

Recruitment to the Study

A total of 457 neonates were screened for possible enrollment into the study. Of these, 28 declined to consent, and 42 neonates died (Supplementary File Table 1 shows their admission characteristics) before the 72-hour blood sample could be obtained, and 65 had incomplete results; therefore, only 322 neonates were enrolled in the study and included in the final analysis. This information is shown in Figure 1.

Prevalence of AKI in Neonates Admitted to NICU

The prevalence of AKI in neonates admitted to NICU at UTH was 13.7% (44/322), with KDIGO stage 1 AKI being the most common stage of AKI (23, 52.3%) at presentation as shown in Figure 1 below.

Baseline Demographic and Clinical Characteristics of the Study Participants

Of the 322 neonates who were enrolled into the study, the majority were males 172 (53.4%). Most of the participants 306 (95.0%) were between 1 and 7 days old. Most participants had a gestational age at delivery of 37 weeks or less (56.5%) and normal birth weight ($\geq$ 2500 g) 172 (53.4%). The prevalence of AKI was significantly higher in younger neonates aged 7 days or less compared to older neonates aged $>$ 8 days (84.1 % vs 15.9%, $P = .002$). The majority of the participants had an Apgar score greater than 6, and the median Apgar score at 5 minutes was 8 (6-9). Having higher ($>$7) Apgar scores was correlated to the greater rate of AKI (86.4% versus 13.6%; $P = .02$). No significant association was observed between the presence of AKI and other demographic characteristics, such as gestation age ($P = .78$), birth weight ($P = .97$), and sex ($P = .63$) (Table 1).

The neonatal admissions were largely referred from other hospitals/clinics (55.3%). The most common presenting complaint at the time of admission was difficulties in breathing (87.6%). Other presenting complaints were fever (18.6%), poor feeding (18.6%), vomiting (2.2%), and seizures (28.6%). There were significantly more neonates that had a history of vomiting in the AKI group compared to the no AKI group (9.1% vs 1.1%; $P = .008$). No significant association was observed between the presence of AKI and other characteristics, such as place of delivery ($P = .74$), mode

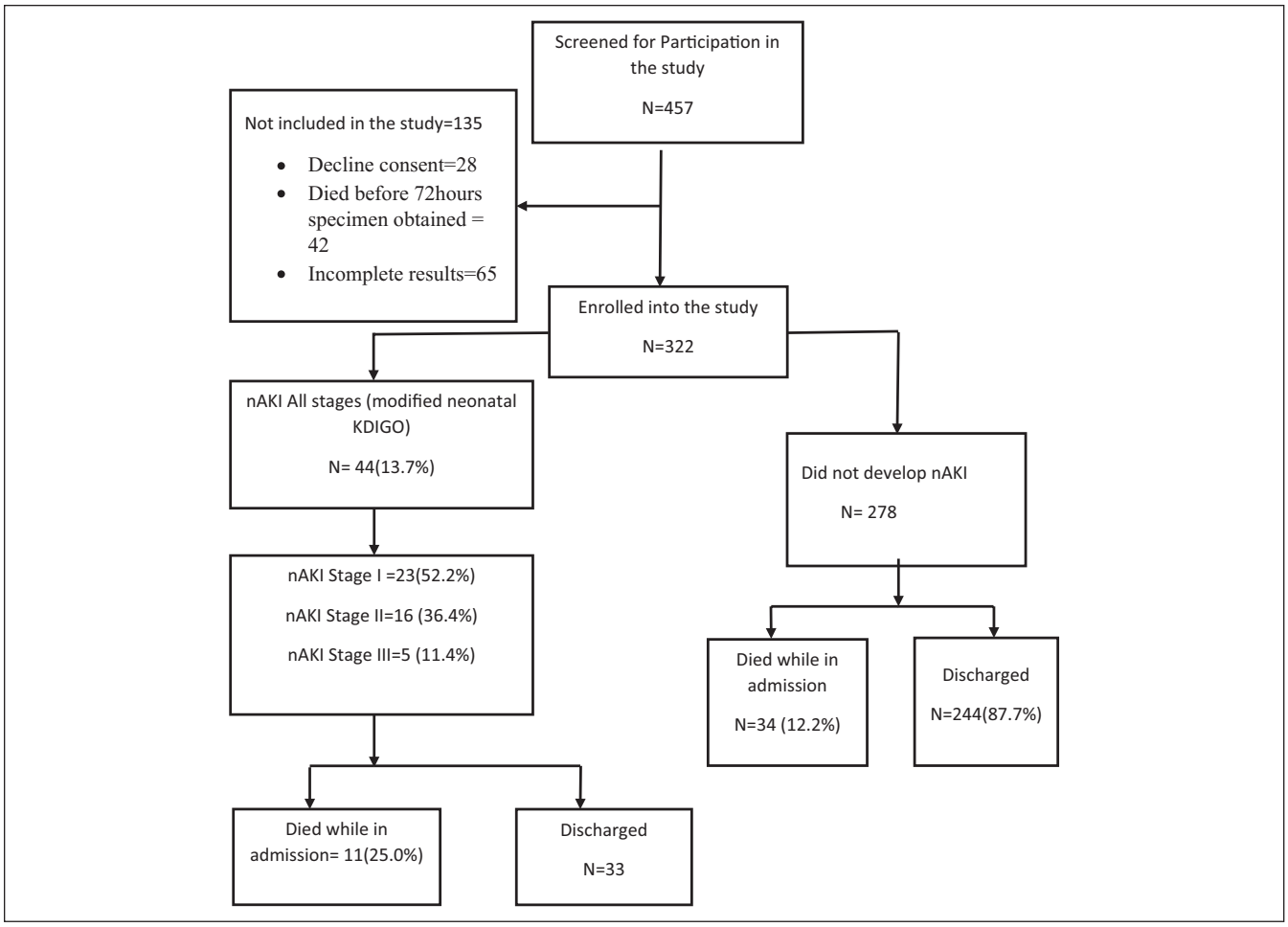

Figure 1. Participants' flowchart.

of delivery ($P=.66$), mode of admission ($P=.23$), fever ($P=.45$), poor feeding ($P=.22$), convulsions ($P=.36$), and respiratory distress ($P=.21$).

The most common primary diagnoses were Hypoxic Ischemic Encephalopathy (HIE) (37.0%), followed by prematurity (35.7%), and then presumed sepsis (16.5%). Whereas the most common secondary diagnoses were presumed sepsis (49.3%) and respiratory distress syndrome (RDS) (37.9%). The presence of AKI did not statistically differ among different levels of secondary diagnosis ($P=.69$). Presumed sepsis ($P=.59$), HIE (0.08), prematurity ($P=.91$), RDS ($P=.60$), congenital syphilis ($P=.60$), neonatal jaundice (NNJ; $P=1.00$), congenital anomaly ($P=.72$), meconium aspiration ($P=1.00$), and PPHN were not associated with the presence of AKI.

The most common antibiotic given to neonates after diagnosis was amikacin in combination with piperacillin/tazobactam (97.8%), followed by meropenem, which was used in 18.6% of neonates. Vasopressor support was used in 18.9% and only 10.9% required mechanical ventilation. The NICU antibiotic protocol based on microbiology surveillance is that the first-line empirical intravenous antibiotics are amikacin which is given together with piperacillin/tazobactam. The second-line empirical antibiotic is either meropenem or ciprofloxacin. All neonates admitted to the NICU receive antibiotics except those admitted for observation, such as the Infants of Diabetic Mothers, who are only admitted for glucose monitoring. Among neonates who were exposed to ciprofloxacin AKI occurred in 11.4% compared to only 2.5% in those without ciprofloxacin exposure ($P=.01$). Similarly, neonates exposed to meropenem were more likely to have AKI compared to the unexposed (43.2% vs 14.7%; $P<.001$). No significant association was observed between the presence of AKI and exposure to other drugs, such as cloxacillin ($P=.07$), amikacin ($P=.06$), and piperacillin/tazobactam ($P=.06$). There was no significant association between the presence of AKI and use of vasopressor support ($P=.49$) or need for mechanical ventilation ($P=1.00$).

No significant differences were observed in laboratory parameters (white blood cells, hemoglobin levels, platelets, and mean corpascular volume [MCV]) between participants with AKI and participants without AKI ($P>.05$) (Supplementary File 1, Table S2).

Table 1. Demographic and Clinical Characteristics of Study Participants ($n = 322$).

Characteristic	Category	AKI present		Total ($N = 322$) (%)	P
		No ($N = 278$)	Yes ($N = 44$)		
Age in days	1-7	269 (96.8%)	37 (84.1%)	306 (95.0)	.002[a]
	8-16	9 (3.2%)	7 (15.9%)	16 (5.0)	
Sex	Male	147 (52.9%)	25 (56.8%)	172 (53.4)	.63[b]
	Female	131 (47.1%)	19 (43.2%)	150 (46.6)	
Gestation age group	Preterm (≤ 37 weeks)	158 (56.8%)	24 (54.5%)	182 (56.5)	.78[b]
	Full term (> 37 weeks)	120 (43.2%)	20 (45.5%)	140 (43.5)	
Birth weight in grams	Normal weight (≥ 2500 g)	148 (53.2%)	24 (54.5%)	172 (53.4)	.97[a]
	Low birth weight (1500-2499 g)	106 (38.1%)	16 (36.4%)	122 (37.9)	
	Very low birth weight (1000-1499 g)	24 (8.6%)	4 (9.1%)	28 (8.7)	
Apgar group	Abnormal score (≤6)	84 (30.3%)	6 (13.6%)	90 (28.0)	.02[b]
	Normal score (≥7)	193 (69.7%)	38 (86.4%)	231 (72.0)	
Mothers age in years	15-25	112 (40.3%)	22 (50.0%)	134 (41.6)	.11[a]
	26-35	144 (51.8%)	16 (36.4%)	160 (49.7)	
	36-47	22 (7.9%)	6 (13.6%)	28 (8.7)	
Maternal diagnosis	Hypertension	38 (13.7%)	5 (11.4%)	43 (13.4)	.33[a]
	Diabetes mellitus	3 (1.1%)	0 (0.0%)	3 (0.9)	
	Urinary tract infection	8 (2.9%)	2 (4.5%)	10 (3.1)	
	Antepartum hemorrhage (APH)	9 (3.2%)	5 (11.4%)	14 (4.3)	
	Premature rupture of membrane	4 (1.4%)	0 (0.0%)	4 (1.2)	
	Malaria	3 (1.1%)	0 (0.0%)	3 (0.9)	
	None	213 (76.6%)	32 (72.7%)	245 (76.1)	
Place of delivery	Hospital	252 (90.6%)	42 (95.5%)	294 (91.3)	.74[a]
	Clinic	17 (6.1%)	1 (2.3%)	18 (5.6)	
	Home	9 (3.2%)	1 (2.3%)	10 (3.1)	
Mode of delivery	Spontaneous vaginal delivery	173 (62.2%)	30 (68.2%)	203 (63.0)	.66[a]
	Assisted vaginal delivery	7 (2.5%)	0 (0.0%)	7 (2.2)	
	Cesarean section delivery	98 (35.3%)	14 (31.8%)	112 (34.8)	
Mode of admission of neonate	Direct admission from WNBH labor ward	128 (46.0%)	16 (36.4%)	144 (44.7)	.23[b]
	Referral from another hospital/clinic	150 (54.0%)	28 (63.6%)	178 (55.3)	
Complaints at admission	Fever	50 (18.0%)	10 (22.7%)	60 (18.6)	.45[b]
	Poor feeding	48 (17.3%)	11 (25.0%)	59 (18.3)	.22[b]
	Vomiting	3 (1.1%)	4 (9.1%)	7 (2.2)	.008[a]
	Any convulsions	82 (29.5%)	10 (22.7%)	92 (28.6)	.36[b]
	Breathing difficulties	246 (88.5%)	36 (81.8%)	282 (87.6)	.21[b]
Primary diagnosis	Presumed sepsis	170 (61.2%)	25 (56.8%)	195 (60.6)	.59[b]
	Hypoxic ischemic encephalopathy (HIE)	108 (38.8%)	11 (25.0%)	119 (37.0)	.08[b]
	Prematurity	105 (37.8%)	17 (38.6%)	122 (37.9)	.91[b]
	Respiratory distress syndrome (RDS)	90 (32.4%)	16 (36.4%)	106 (32.9)	.60[b]
	Congenital syphilis	7 (2.5%)	0.0%	7 (2.2)	.60[a]
	Neonatal jaundice (NNJ)	18 (6.5%)	2 (4.5%)	20 (6.2)	1.00[a]
	Congenital anomaly	15 (5.4%)	3 (6.8%)	18 (5.6)	.72[a]
	Meconium aspiration	6 (2.2%)	1 (2.3%)	7 (2.2)	1.00[a]
	Persistent pulmonary hypertension (PPHN)	19 (6.8%)	3 (6.8%)	22 (6.8)	1.00[a]

(continued)

Table 1. (continued)

Characteristic	Category	AKI present		Total (*N* = 322) (%)	*P*
		No (*N* = 278)	Yes (*N* = 44)		
Antibiotic exposure	Vancomycin	6 (2.2%)	0 (0.0%)	6 (1.9)	1.00[a]
	Cloxacillin	8 (2.9%)	4 (9.1%)	12 (3.7)	.07[a]
	Amikacin/piperacillin/tazobactam	274 (98.6%)	41 (93.2%)	315 (97.8)	.06[a]
	Ciprofloxacin	7 (2.5%)	5 (11.4%)	12 (3.7)	.01[a]
	Meropenem	41 (14.7%)	19 (43.2%)	60 (18.6)	<.001[b]
Use of ionotropic support	*n* (%) Yes	51 (18.3%)	10 (22.7%)	61 (18.9)	.49[b]
Need for mechanical ventilation (MV)	*n* (%) Yes	30 (10.8%)	5 (11.4%)	35 (10.9)	1.00[a]
Admission creatinine	Median (Q1-Q2)	86.0 (68.0-103.8)	59.5 (47.0-77.7)		<.001[c]
Day 3 creatinine	Median (Q1-Q2)	65.0 (53-82)	117 (98.0-159.0)		<.001[c]
Length of hospital stay (days)	Short (0-5)	113 (40.6%)	14 (31.8%)	127 (39.4)	.001
	Medium (6-10)	126 (45.3%)	14 (31.8%)	140 (43.5)	
	Long (>10)	39 (14.0%)	16 (36.4%)	55 (17.1)	
Final outcome	Death	34 (12.3%)	11 (25.0%)	45 (14.0)	.02
	Discharge	243 (87.7%)	33 (75.0%)	276 (86.0)	

Note. RDS = respiratory distress syndrome; PPHN = persistent pulmonary hypertension; NNJ = neonatal jaundice; HIE = hypoxic ischemic encephalopathy; MV =mechanical ventilation.
[a]Fisher's exact test.
[b]Chi-square test.
[c]Mann–Whitney Test.

Multivariable Logistic Regression on Risk Factors of AKI in Neonates Admitted to NICU

Univariate and multivariable logistic regression analyses were performed to identify significant factors associated with AKI in neonates admitted to the NICU. The results of the univariate analysis in Table 2 showed that age in days, Apgar scores, maternal illness, vomiting, use of amikacin/piperacillin/tazobactam, ciprofloxacin, and use of meropenem were associated with AKI ($P < .05$).

After multivariable logistic regression, identified predictors of AKI were an Apgar score greater than 6, maternal antepartum hemorrhage, neonatal vomiting as the presenting complaint, and exposure to antibiotics meropenem and ciprofloxacin (Table 2).

Outcomes

There was a significant association between the status of AKI and the final patient outcome ($P = .02$) (Table 1). The proportion of deaths was significantly higher in neonates with AKI (25.0%) compared to those who did not have AKI (12.3%). There was also a significant association between AKI and length of hospital stay, as those with AKI (36.4%) had a higher proportion of participants who spent more than 10 days in hospital than those without AKI (14.0%). In addition, the proportion of deaths among neonates with stage 3 AKI (80.0%) was significantly higher than among neonates with stage 2 AKI (25.0%), stage 1 AKI (13.0%), and without AKI (12.3%) (Supplementary File 1, Table S3).

Multivariable Logistic Regression: Predictors of Poor Outcome

The risk of mortality for patients in this cohort was higher for neonates with an Apgar score ≤ 6 (AOR 0.24; 95% CI: [0.09-0.68], $P = .007$), neonates with birth weight between 1000 and 1499 g (AOR 11.48; 95% CI: [2.30-57.2], $P = .003$), and neonates with AKI (AOR 3.69; 95% CI: [1.44-9.46], $P = .007$). Other risk factors were the presence of congenital anomalies and neonates with persistent pulmonary hypertension (Table 3).

Discussion

This prospective cohort study was conducted from 2021 to 2022, to determine the prevalence, risk factors, and short-term outcomes of nAKI among neonates admitted to a low-resource NICU. A total of 322 neonates were enrolled. AKI, was present in about 13% and was associated with longer length of hospital stay and higher mortality. Antepartum hemorrhage, and use of meropenem and ciprofloxacin were associated with high risk of AKI. Surprisingly, many of the traditional AKI risk factors, such as low Apgar score,

Table 2. Multivariable Logistic Regression on Risk Factors of AKI in Neonates Admitted to NICU ($n = 322$).

	Crude OR (95% CI)	Adjusted OR (95% CI)	*P*
Apgar group			
Abnormal score (≤6)	Ref	Ref	
Normal score (>6)	2.76 [1.12-6.79]	2.69 [1.04-6.93]	.04
Maternal illness			
None	Ref	Ref	
Hypertension	0.88 [0.32-2.39]	1.16 [0.40-3.4]	.79
Urinary tract infection	1.66 [0.34-8.19]	1.02 [0.18-5.73]	.98
Antepartum hemorrhage	3.70 [1.1-11.73]	5.58 [1.63-19.13]	.006
Any vomiting			
No	Ref	Ref	
Yes	9.17 [1.99-42.47]	5.76 [1.10-30.32]	.04
Ciprofloxacin			
No	Ref	Ref	
Yes	4.96 [1.5-16.41]	4.53 [1.22-16.84]	.02
Meropenem			
No	Ref		
Yes	4.39 [2.22-8.69]	4.37 [1.97-9.69]	<.001

Note. Model statistics. OR = odds radio; CI = confidence interval.
Nagelkerke $R^2 = 0.21$, Cox-Snell $R^2 = 0.12$.
Testing Global Null Hypothesis: omnibus of model coefficient $\chi^2 = 40.09$, $df = 10$, $P < .001$. Hosmer and Lemeshow Goodness-of-Fit Test: $\chi^2 = 3.694$, $df = 6$, $P = .72$.

Table 3. Multivariable Logistic Regression: Predictor of Death in Neonates Admitted to NICU ($n = 322$).

	Crude OR (95% CI)	Adjusted OR (95% CI)	*P*
Apgar group			
Abnormal score (≤6)	Ref	Ref	
Normal score (>6)	0.34 [0.18-0.64]	0.24 [0.09-0.68]	.007
Birth weight (g)			
≥2500	Ref	Ref	
1500-2499	0.53 [0.26-1.09]	2.74 [0.99-7.55]	.05
1000-1499	0.82 [0.26-2.53]	11.48 [2.30-57.2]	.003
Presence of AKI			
No	Ref	Ref	
Yes	2.38 [1.10-5.15)	3.69 [1.44-9.46]	.007
Amikacin			
No	Ref	Ref	
Yes	0.058 [0.01-0.31]	0.01 [0.001-0.076]	<.001
Hypoxic ischemic encephalopathy			
No	Ref		
Yes	1.79 [0.95-3.38]	3.60 [1.07-12.09]	.04
Congenital anomaly			
No	Ref	Ref	
Yes	4.44 [1.6-12.15]	32.53 [8.30-127.45]	<.001
Persistent pulmonary hypertension			
No	Ref	Ref	
Yes	7.79 [3.14-19.34]	19.63 [5.80-66.43)	<.001

Note. Model statistics. OR = odds radio; CI = confidence interval; AKI = acute kidney injury.
Nagelkerke $R^2 = 0.36$, Cox-Snell $R^2 = 0.20$.
Testing Global Null Hypothesis: omnibus of model coefficient $\chi^2 = 72.5$, $df = 8$, $P < .001$. Hosmer and Lemeshow Goodness-of-Fit Test: $\chi^2 = 8.39$, $df = 6$, $P = .21$.

mechanical ventilation, and sepsis, were not shown to be associated to AKI in our cohort. We attribute this to the fact that our cohort enrolled few neonates with these risk factors but also raises the possibility of inaccurate Apgar score assignment.

AKI occurred in 13.7% of all neonates who were enrolled. This is lower than the prevalence reported in similar studies conducted in Tanzania (31.5%)[12] and Pakistan (37.6%).[14] This lower prevalence could be because, in contrast to our cohort, these 2 studies recruited more neonates who were critically ill. In our setting, most of the term neonates with late onset neonatal sepsis are not admitted to the NICU but rather are referred to the Children's Hospital. Interestingly, a study conducted in a western Indian NICU reported an even lower prevalence of AKI (4.2%).[15] This study did not use the modified neonatal KDIGO definition.

The most common AKI severity grade in our cohort was KDIGO stage 1. This is consistent with prior research from other countries, which found that stage 1 AKI was the most common among neonates.[12,16] Despite this, our study showed that nAKI is not uncommon in the NICU and even mild AKI is associated with increased mortality and prolonged hospital stay.

Early identification of the populations at the highest risk of developing AKI is the key to improving AKI outcomes.[4] In this cohort, there were more male compared to female neonates who had AKI which is similar to the findings by Silvana et al in Macedonia and Halder et al in Bangladesh.[1,17] Congenital anomalies of the kidney and urinary tract are more common in boys and may increase their risk of AKI.

Surprisingly, nAKI was associated with higher Apgar scores in contrast to previous studies.[15,18] There are several possible reasons for this. Firstly, the cohort was skewed. As a consequence of limited space in the NICU at UTHs-WNBH, the majority of term babies with neonatal sepsis are referred to the children's hospital for treatment. Secondly, about 10% of all children screened died before the 72-hour blood specimen could be obtained. This means that many of the sickest neonates were not included in the final data analysis. Finally, our result may be a reflection of inaccurately assigned 5-minute Apgar scores.[19-22] This may especially occur in settings with low resources and staffing. However, 1 Kenyan study found that health worker factors associated with inaccurate scores include lack of access to Apgar scoring charts, neonatal resuscitation, and instrumental delivery.[23]

Furthermore, the risk of developing AKI was higher in neonates who presented with vomiting on admission compared to neonates without vomiting. Vomiting is a known risk factor for volume loss or dehydration, which in turn has been associated with AKI in previous studies.[24,25] Some of the variables, including vomiting, that were found to be correlated to AKI in this cohort only occurred in a small proportion of participants. Thus, despite statistically significant *P*-values, confidence intervals were quite wide.

There is evidence in the literature that a number of antibiotics can have an effect on the development of AKI.[12,26] One reason for this is that patients receiving these antibiotics may already be at high risk of AKI due to underlying conditions and disease severity, in addition to the direct renal effects of specific drugs.[26] This study showed that exposure to antibiotics, such as ciprofloxacin, was associated with an increased risk of developing AKI among neonates. Meropenem was another antibiotic that was associated with an increased likelihood of developing AKI in neonates. Neonates who received either meropenem or ciprofloxacin were critically ill as these are the second-line empirical antibiotics in our unit. It is likely that the AKI seen the neonates exposed to these drugs is due not to the drugs themselves but rather to the underlying disease since these antibiotics are used as second-line antimicrobials in our unit and so neonates receiving them are more likely to be sicker and therefore at higher risk of AKI.

We found that sepsis, mechanical ventilation, prematurity, and respiratory distress syndrome were not associated with the occurrence of AKI in contrast to previous studies.[27,28] These covariates were not included in the regression model due to the small numbers in each sub-group and this reduced the power to detect any associations.

The duration of hospital stay was longer in participants with AKI which is consistent with findings from previous studies.[28-30] Literature suggests that the duration of stay is longer for neonates with higher stages of AKI (stages 2 and 3).[9,31] Prolonged hospital stay seriously impacts the costs of health care provision especially in resource-constrained environments like ours.

Tembo et al[32] conducted a retrospective analysis in our unit 5 years ago and found that facility-based neonatal mortality rate was at 40.2% with low birth weight and congenital anomalies being associated with an increased risk of mortality which was similar to our findings.

Similar to previous reports, the proportion of neonates who died was significantly higher among neonates with AKI as compared to those without AKI and this effect was greater the higher the AKI stage.[28-30] AKI management remains a challenge particularly in low-resource centers due to limitations in diagnostic capacity and scarcity of age-appropriate kidney replacement therapy modalities.

The other predictors of mortality among this cohort were HIE, congenital anomalies, PPHN, and a birth weight that is less than 2500 g similar to the findings in Ethiopia and Australia.[33,34] Factors that may contribute to a higher risk of mortality in low birth weight neonates include RDS, hypothermia, feeding difficulties, and increased susceptibility to infection.[35,36] Tembo et al[32] conducted a retrospective analysis in our unit 5 years ago and found that facility-based neonatal mortality rate was at 40.2% with low birth weight and congenital anomalies being associated with an increased risk of mortality which was similar to our findings.

Although the study presents important findings, there are limitations, mainly related to the sample size in the subgroups. Due to the small numbers of neonates presenting with certain independent variables, most of the covariates were either not included in the model or were not significant. As a result, some associations with other variables were not examined. Therefore, further studies with larger sample sizes are needed to determine whether certain factors are associated with AKI. Another limitation in this study was that urine output was not used in the determination of AKI due to challenges in collection of urine samples in the neonates. The third limitation is that SCr was not done on a daily basis and as a result, some neonates may have been missed if AKI occurred between days 3 and 6. The use of the Jaffe method for measuring SCr is highly influenced by chromogens including bilirubin values which was not part of the study variables that forms another limitation. None of the neonates who developed AKI had a kidney, ureter, and bladder ultrasound done to exclude any possibility of renal abnormalities that may not be overt or renal vein thrombosis which is the commonest cause of AKI in neonates. Additionally, there was no long-term follow-up of the neonates that developed AKI. These patients were only followed-up for 30 days. The lack of use of Neonatal illness severity score was another limitation in this study.

Conclusion

The study showed that AKI is not uncommon in neonates admitted to intensive care units even though most neonates only had mild AKI (stage 1). Regardless of the fact that majority only had mild AKI, there was still an increased associated mortality and increased duration of hospital stay in the intensive care unit. Identified risk factors of AKI were being delivered from mothers with APH and receiving either meropenem or ciprofloxacin. Further studies on NICU subpopulations are required to shade more light on nAKI in our setting.

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Author Contributions

M.C., S.M.M., and C.M. contributed to conceptualization of the study. M.C. involved in data collection, data analysis, and curation. M.C., S.M.M., and C.M. participated in writing—original manuscript draft and writing—review and editing.

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Supplemental Material

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